Attorney's Docket No.: 003301-212
Patent No.: 5,656,667
Application No.: 08/471,200

#15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:

Harald BREIVIK et al.

Application No.: 08/471,200

Patent No.: 5,656,667

Filed: June 6, 1995

For: FATTY ACID COMPOSITION

MAIL STOP: PATENT EXTENSION

APPLICATION FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. § 156

MAIL STOP: PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

In accordance with the provisions of 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, the owner (Pronova Biocare AS) of U.S. Patent No. 5,656,667 requests that the term of this patent be extended by **1,477 days** to expire on **August 28, 2018**.

U.S. Patent No. 5,656,667 was filed on **June 6, 1995** (*i.e.*, U.S. Application No. 08/471,200) and issued on **August 12, 1997** for "Fatty Acid Composition," to Harald Breivik, Bernt Börretzen, Knut H. Dahl, Hans Einar Krokan, and Kaare Harald Bönaa ("Breivik et al."). The term of U.S. Patent No. 5,656,667 will expire, unless extended, on **August 12, 2014** (*i.e.*, seventeen years from the date the patent was granted in the United States). The above-referenced patent is a continuation of U.S. Application No. 07/902,500, filed on June 23, 1992 (now U.S. Patent No. 5,502,077), which is a continuation of U.S. Application No. 07/389,902, filed August 4, 1989, now abandoned.

Pronova Biocare AS, a Norwegian Corporation, is the assignee of the entire right, title and interest in U.S. Patent No. 5,656,667, granted to Breivik et al., on August 12, 1997 for

"Fatty Acid Composition," by virtue of an assignment from the inventors to Norsk Hydro a.s, of Bygdøy Allé 2, 0257 Oslo 2, Norway recorded on August 4, 1989, at Reel/Frame 005111/0097 in the grandparent application 07/389,902, filed August 4, 1989 (APPENDIX E). The assignment from Norsk Hydro a.s to Pronova Biocare AS was submitted to the Patent Office on August 11, 2004. A copy of the submitted assignment documents are attached (APPENDICES E and F respectively). The document is yet to be recorded and issued an official reel and frame number.

Ross Products Division, Abbott Laboratories is the marketing agent ("Ross Products Division"). A licensing agreement between Ross Products Division and Pronova Biocare exists. Ross Products Division prepared the submissions for the Food and Drug Administration for OMACOR® Capsules, as submitted in NDA application 21-654. Evidence of the agreement between the marketing applicant and Pronova Biocare will be furnished upon request, if required.

Pronova Biocare AS submits this application for extension of the patent term of U.S. Patent No. 5,656,667 by providing the following information in accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, and follows the numerical format set forth in 37 C.F.R. § 1.740(a)(1)-(16). The undersigned attorney has power in this case to act on behalf of Pronova Biocare AS as shown in the Power of Attorney (APPENDIX G).

Also enclosed with the original and each of the three copies are the following documents:

APPENDIX A	Copy of product information about OMACOR® Capsules
APPENDIX B	Copy of approval letter from the FDA for OMACOR® Capsules
APPENDIX C	Copy of U.S. Patent No. 5,656,667
APPENDIX D	Copy of maintenance fee statements for U.S. Patent No. 5,656,667
APPENDIX E	Copy of recorded assignment documents for U.S.S.N. 07/389,902

APPENDIX F	Copy of Request for recordation of assignment and Assignment from Norsk Hydro a.s to Pronova Biocare AS regarding U.S. Patent No. 5,656,667
APPENDIX G	Copy of Power of Attorney

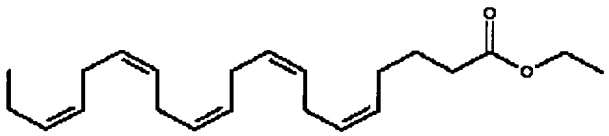
I. 37 C.F.R. § 1.710 (a)(1) TO (a)(15)

(1) IDENTIFICATION OF PRODUCT

The product subject to regulatory review is OMACOR® Capsules (trade name). Product information regarding OMACOR® Capsules is found in APPENDIX A.

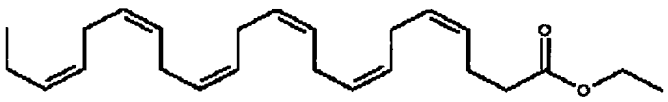
OMACOR® Capsules are compositions comprising a lipid-regulating agent and are supplied as a liquid-filled gel capsules for oral administration. OMACOR® Capsules contain 1 gram of omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl ester. Each capsule provides approximately 465 mg Eicosapentaenoic acid ("EPA") ethyl ester and approximately 375 mg Docosahexaenoic acid ("DHA") ethyl ester.

The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

OMACOR® Capsules also contain the inactive ingredients of: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell). The recommended daily dose is 4 g per day, administered as a single dose or administered twice daily (as 2 capsules of 2 gram each).

OMACOR® Capsules reduce very high (> 500 mg/dl) triglyceride (TG) levels in adult patients. Omega-3 polyunsaturated fatty acids have an effect on hypertension and serum cholesterol.

(2) IDENTIFICATION OF FEDERAL STATUTE/PROVISION OF LAW

OMACOR® Capsules are subject to regulatory review under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355), as a human drug.

(3) DATE ON WHICH PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR SALE

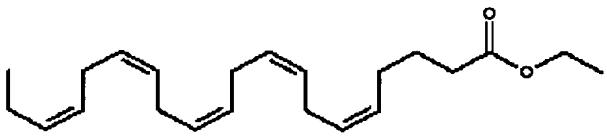
OMACOR® Capsules received permission for commercial marketing under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355), on **November 10, 2004**. A copy of the approval letter is attached as APPENDIX B.

(4) IDENTIFICATION OF EACH ACTIVE INGREDIENT

37 C.F.R. § 1.740(a)(4) requires that in the case of a drug product "an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, the Public Health Service Act, or the Virus Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."

OMACOR® Capsules are a composition comprising a lipid-regulating agent and supplied as a liquid-filled gel capsule for oral administration. OMACOR® Capsules contain 1 gram of omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl ester. Each capsule provides approximately 465 mg Eicosapentaenoic acid ("EPA") ethyl ester and approximately 375 mg Docosahexaenoic acid ("DHA") ethyl ester.

The structural formula of EPA ethyl ester is:



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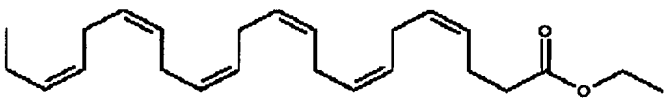


The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

OMACOR® Capsules also contains the inactive ingredients of: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell). The recommended daily dose is 4 g per day, administered as a single dose or administered twice daily (as 2 capsules of 2 gram each).

OMACOR® Capsules reduce very high (> 500 mg/dL) triglyceride (TG) levels in adult patients. Omega-3 polyunsaturated fatty acids have an effect on hypertension and serum cholesterol.

The active ingredients have not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, the Public Health Service Act, or the Virus Serum-Toxin Act.

(5) TIME PERIOD FOR SUBMITTING APPLICATION

This application is submitted within the sixty-day period permitted for submission pursuant to § 1.720(f). Specifically, this application is being submitted within the sixty-day period "beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred."

OMACOR® Capsules received permission for commercial marketing under the Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on **November 10, 2004**. A copy of the approval letter is attached in APPENDIX B. Sixty days from November 10, 2004 is January 9, 2005. However, as January 9, 2005 falls on a Sunday, according to 37 C.F.R. § 1.7, the deadline is extended to Monday, January 10, 2005.

Thus, the last day on which this application could be submitted is **January 10, 2005.**

(6) IDENTIFICATION OF PATENT

The patent for which patent term extension is being sought is U.S. Patent No. 5,656,667, which was filed on June 6, 1995 (U.S. Application No. 08/471,200) and issued on August 12, 1997 for "Fatty Acid Composition," to Harald Breivik, Bernt Börretzen, Knut H. Dahl, Hans Einar Krokan, and Kaare Harald Bönaa, the named inventors. U.S. Application No. 08/471,200 is a continuation of U.S. Application No. 07/902,500 filed June 23, 1992 (now U.S. Patent No. 5,502,077), which is a continuation of U.S. Application No. 07/389,902 filed August 4, 1989, now abandoned.

The term of U.S. Patent No. 5,656,667 will expire, unless extended, on August 12, 2014 (*i.e.*, seventeen years from the date the patent was granted in the United States). It is noted that 20 years from the filing date, given the grandparent application (U.S. Application No. 07/389,902) was filed August 4, 1989, would be August 4, 2009. Thus, the longer of 17 years from issue or 20 years from filing is **August 12, 2014**.

(7) COPY OF PATENT

A copy of U.S. Patent No. 5,656,667 is attached as APPENDIX C.

(8) OTHER PATENT DOCUMENTS

The records of the undersigned do not indicate that any disclaimer or reexamination has been issued in U.S. Patent No. 5,656,667. A Certificate of Correction was issued in U.S. Patent No. 5,656,667 and accompanies the copy of the patent submitted herewith (APPENDIX C).

The four-year and eight-year maintenance fees have been paid. A copy of the maintenance fee statements (from the U.S. Patent &Trademark Office Website) verifying each payment is attached as APPENDIX D.

(9) CLAIMS COVERING THE PRODUCT

The claims of U.S. Patent No. 5,656,667 are directed to methods of treatment and composition claims. Certain of these claims cover the approved product, OMACOR® Capsules.

As required, Applicant provides a showing of at least one applicable method of use claim and one applicable composition claim and the manner in which the claims read on the approved product. Claim 1 is a method for elevating HDL; Claim 14 is a composition claim. Both Claims 1 and 14 read upon the approved product.

Claims of U.S. Pat. No. 5,656,667	OMACOR® Capsules
1. A method for elevating the HDL cholesterol level in the serum of a human patient, which comprises administering to the patient a pharmaceutical composition in which the active ingredients consist essentially of a mixture of fatty acids of which at least 80% by weight is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, said composition being administered in amounts providing a daily dosage of 1 to 10 grams of said mixture of fatty acids.	OMACOR ® Capsules are indicated for treating hypertriglyceridemia (HTG) and were shown to increase the median HDL levels. *See* APPENDIX A. The active ingredients include EPA and DHA which are long chain omega-3 fatty acids which are present in the amounts of approximately 46.5% (465 mg of 1 g) and approximately 37.5% (375 mg of 1 g) respectively. EPA and DHA are present in a weight ratio of 1.24:1, which fulfills the criteria of a weight ratio of from 1:2 to 2:1. The OMACOR® Capsule is 1 g and administered in a daily dosage of 4 g per day (3.6 g fatty acids per day). *See* APPENDIX A.

Claims of U.S. Pat. No. 5,656,667	OMACOR® Capsules
14. A pharmaceutical mixed-fatty-acids composition in which	APPENDIX A and C indicated that OMACOR® Capsules are a mixture of fatty acids.
a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and	OMACOR® Capsules are a pharmaceutical composition, which contain approximately 465 mg EPA and approximately 375 mg DHA in a capsule of 1 gram. The combination of EPA and DHA thus gives approximately 840 mg, *i.e.* approximately 84% by weight, which fulfills the criteria "at least 80% by weight." EPA and DHA are present in a weight ratio of 1.24:1, which fulfills the criteria "in a weight ratio of EPA:DHA of from 1:2 to 2:1."
b) (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight.	An OMACOR® Capsule contains about 1.8% of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid (HPA) (18 mg out of 1 g), and thus fulfills the criteria of at least 1% HPA.

Applicant submits that Claims 1-11, 14-20, 23-24, 26, 28, 30-33, 35, 38-44, 47-48, 53-54, 56, 59, and 61-62 all read on the approved product.

Applicant believes that Claims 12, 13, 21-22, 27, 29, 34, 36, 37, 45, 46, 49-52, 55, and 60 may also read upon the approved product. In particular, Claims 12, 13, 27, 36, 37, 45, 46, 55, and 60 relate to the salt form or free acid form of the fatty acids. Applicant believes these particular claims may read upon the approved product because, for instance, salt forms are included under the definition of a "product" under 35 U.S.C. § 156(f). *See Pfizer Inc. v. Dr. Reddy Labs. Ltd.*, 359 F.3d 1361, 1364-66, 69 U.S.P.Q.2d 2016, 2018-2019 (Fed. Cir. 2004). In the *Pfizer* case, the Federal Circuit concluded that the statute makes clear that the drug product means the active ingredient, which includes any salt or ester of the active ingredient. *Id.*

(10) RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. § 156(g)

The relevant dates and information pursuant to 35 U.S.C.: § 156(g), and 37 C.F.R. § 1.740(a)(10)(i), to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for a patent claiming a human drug are as follows:

(a) *The effective date of the investigational new drug (IND) application and the IND number*: The IND application, **IND 45,998**, was submitted by Pronova Biocare AS on **August 15, 1994.**

(b) *The date on which a new drug application (NDA) was initially submitted and the NDA number*: The NDA was initially submitted on **January 12, 2004**. The application number was **NDA 21-654**.

(c) *The date on which the NDA was approved*: **November 10, 2004**. *See* APPENDIX B.

(11) BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES

The following is a brief description of the significant activities undertaken by the Applicant and the marketing applicant during the applicable regulatory review period with respect to OMACOR® Capsules and the significant dates applicable to such activities.

Date	To[1]	From	Type	Summary
August 15, 1994[1]	FDA	Pronova	Submission	IND application regarding HTG filed, IND 45,998.
October 19, 1994	Pronova	Consultant[3]	Facsimile	Report concerning FDA contact; protocol amendment to alter sTG levels after dietary intervention portion of trial.
November 20, 1995	FDA	Pronova	Annual Progress Report	Annual progress report that covers the period from September 12, 1994 to September 12, 1995.
December 18, 1995	Pronova	Consultant	Report	Call from and to FDA's Dr. Sheen. Copy of FDA contact report.
February 23, 1996	Pronova	FDA	Letter	FDA requires more information regarding toxicity studies, including rat and mouse carcinogenicity studies.
March 14, 1996			Meeting	Pre-NDA meeting, Metabolic & Endocrine div. (FDA and Pronova).
April 5, 1996	Pronova	Consultant	Minutes	Minutes regarding the Pre-NDA meeting, Metabolic & Endocrine div.
October 18, 1996	Pronova	FDA	Minutes	Additional minutes regarding the Pre-NDA meeting, Metabolic & Endocrine div.
November 24, 1996	Pronova	Consultant	Facsimile	Draft annual report for triglyceride IND 45,998. Covers the period from August 12, 1995 to August 31, 1996.
January 5, 1997	Pronova	Consultant	Facsimile	Concerning Pronova's facsimiles of the 12th and 18th of December 1996; FDA toxicity questions.

Date	To[1]	From	Type	Summary
January 27, 1997	Pronova	FDA	Facsimile	Response to questions from FDA regarding the toxicology review (rat and mouse carcinogenicity studies) on OMACOR® Capsules.
February 14, 1997	Pronova	Consultant	Facsimile	Toxicity diskettes (FDA wants another copy of the tox diskette), tox information.
February 20, 1997	Pronova	Covance[2]	Letter	Oncogenicity studies in rats and mice. Additional copies of the FDA diskettes.
March 4, 1997	Pronova	FDA	Facsimile	Response to questions from FDA regarding the toxicology review (rat and mouse tumorogenicity studies) on OMACOR® Capsules.
August 7, 1998	Pronova	Consultant	E-mail	Confirmation of meeting at Pronova and agenda regarding toxicology studies and CMC.
October 17, 2000	Covance	Pronova	Facsimile	Data regarding oncogenicity studies are sent.
December 12, 2000	Pronova	Covance	Facsimile	Data regarding oncogenicity studies are acknowledged.
October 31, 2001			Meeting	Pre-NDA meeting, Metabolic & Endocrine div.
April 19, 2002	FDA	Ross	Letter	Submissions of review regarding published literature on the effects of omega-3 fatty acid treatment on cardiovascular clinical outcomes.
June 13, 2002			Minutes	Teleconference, Metabolic & Endocrine Division.
July 30, 2003	Ross	FDA	Telephone call	Ross and FDA discusses issues regarding filing of new drug application.
August 13, 2003	FDA	Ross	Facsimile	Ross requests a conference call with the reviewing Medical Officer, Chemistry Reviewer, and Biometrics Reviewer to discuss issues pertaining to NDA 21-654. Additional information regarding CMC/stability of batches is attached.

Date	To[1]	From	Type	Summary
September 10, 2003	Ross	FDA		Amendments which were requested in teleconference regarding additional information regarding OMACOR® Capsules are attached.
October 20, 2003			Minutes	Teleconference, Metabolic & Endocrine Division.
January 9, 2004	FDA	Ross	Submission	NDA 21-654 is filed with the Metabolic & Endocrine Division.
January 12, 2004	FDA		Receipt of document	FDA receives NDA 21-654.
January 20, 2004	FDA	Ross	Submission	
March 25, 2004	Ross	FDA	Letter	Acknowledgement from FDA that the NDA application was sufficiently complete to permit a substantive review.
April 2, 2004	FDA	Ross	Submission	
May 10, 2004	FDA	Ross	Submission	
May 12, 2004	FDA	Ross	Submission	
May 24, 2004	FDA	Ross	Submission	
May 28, 2004	FDA	Ross	Submission	Certificate of analysis.
June 2, 2004	FDA	Ross	Submission	
July 1, 2004	FDA	Ross	Submission	
July 20, 2004	FDA	Ross	Submission	
August 17, 2004	FDA	Ross	Submission	
September 2, 2004	FDA	Ross	Submission	
September 3, 2004	FDA	Ross	Submission	
September 8, 2004	FDA	Ross	Submission	
September 10, 2004	FDA	Ross	Submission	
September 14, 2004	FDA	Ross	Submission	
September 17, 2004	FDA	Ross	Submission	
September 21, 2004	FDA	Ross	Submission	
September 24, 2004	FDA	Ross	Submission	
September 29, 2004	FDA	Ross	Submission	
October 5, 2004	FDA	Ross	Submission	
October 18, 2004	FDA	Ross	Submission	
October 21, 2004	FDA	Ross	Submission	
October 22, 2004	FDA	Ross	Submission	
October 28, 2004	FDA	Ross	Submission	
October 29, 2004	FDA	Ross	Submission	
November 1, 2004	FDA	Ross	Submission	
November 8, 2004	FDA	Ross	Submission	
November 9, 2004	FDA	Ross	Submission	

Date	To[1]	From	Type	Summary
November 10, 2004	Ross/ Pronova	FDA	Letter	FDA approves NDA 21-654.
November 11, 2004	Ross/ Pronova		Letter	Ross/Pronova receives FDA approval of NDA 21-654.

[1] The IND application (IND 45,998) was submitted by Pronova Biocare AS on August 15, 1994. In accordance with a license agreement between Pronova Biocare AS (licensor) and Ross Products Division (licensee), Ross Products Division filed an NDA application with the FDA on January 12, 2004. The NDA application was approved November 10, 2004.

[2] Covance has performed and reported several studies on animal toxicology of OMACOR® Capsules on behalf of Pronova Biocare AS.

[3] Consultant Ronald G. Leonardi (President, R&R Registrations for Pronova Biocare AS).

(12) ELIGIBILITY FOR EXTENSION OF PATENT TERM

In the opinion of Pronova Biocare AS, U.S. Patent No. 5,656,667 is eligible for the requested extension of patent term, and the extension is **1,477 days**.

The length of the extension of the term of U.S. Patent No. 5,656,667 of **1,477 days** is based upon 37 C.F.R. § 1.775, which states that the term of the patent for a human drug will be extended by the length of the regulatory review period for the product as determined by the Secretary of Human Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(l) through (d)(6) of this section.

12.1 37 C.F.R. § 1.775(c)

First, the length of the regulatory review period for a human drug will be determined by the Secretary of Human Health and Human Services. Under 35 U.S.C. § 156(g)(3)(B), it is the sum of:

> (1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date an application was initially submitted for such product under those sections; and
>
> (2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 505 of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section.

12.2 37 C.F.R. § 1.775(c)(1)

With respect to 37 C.F.R. § 1.775(c)(1), the date a clinical investigation started was **August 15, 1994**. The date the new drug application was initially submitted with respect to section 505 of the Federal Food, Drug and Cosmetic Act was **January 12, 2004**.

Thus, the "number of days in the period beginning on the date an exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date an application was initially submitted for such product under those sections" is the number of days between **August 15, 1994** and **January 12, 2004**, which is **3,438 days** (*i.e.*, 9 years and 152 days).

12.3 37 C.F.R. § 1.775(c)(2)

With respect to 37 C.F.R. § 1.775(c)(2), the date the application was initially submitted with respect to section 505 of the Federal Food, Drug and Cosmetic Act was **January 12, 2004**. The date this application was approved under such act was **November 10, 2004**.

Thus, the "number of days in the period beginning on the date the application was initially submitted for the approved product under section 505 of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section" is the number of days between **January 12, 2004** and **November 10, 2004**, which is **304 days**.

Thus, the sum of the periods in (c)(1) and (c)(2) of this paragraph is **3,742 days** (*i.e.*, 10 years and 90 days).

12.4 37 C.F.R. § 1.775(d)

Next, the regulatory review period for the product, as determined by the Secretary of Human Health and Human Services, is reduced as appropriate pursuant paragraphs (d)(1) through (d)(6) of 37 C.F.R. § 1.775(d). At the outset, we note that 37 C.F.R. § 1.775(d)(6) is not applicable, since US Patent No. 5,656,667 was not "issued before September 24, 1984."

37 C.F.R. § 1.775(d)(1)(5) states:

The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by-

(1) Subtracting the number of days determined by Secretary of Human Health and Human Services the to be in the regulatory review period:
  (i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued:
  (ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Human Health and Human Services that the applicant did not act with due diligence;
  (iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;
(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;
(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health and Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug and Cosmetic Act;
(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;
(5) If the original patent was issued after September 24, 1984,
  (i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and
  (ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

12.5 37 C.F.R. § 1.775(d)(1)

The periods in paragraph d(1) are calculated as follows:

(i) The number of days in the period of paragraph (c)(1) which was on and before the date on which the patent issued is **1,093 days** (*i.e.*, period between the day the IND was filed, **August 15, 1994**, to the day the patent issued on **August 12, 1997**). The number of days in the period of paragraph (c)(2) of this section which were on and before the date on which the patent issued is **zero (0) days** (*i.e.*, the

patent issued on August 12, 1997; the NDA application was filed January 12, 2004, after issuance of the patent.).

(ii) From August 7, 1998 to October 17, 2000, there is no activity. However, as there is no means by which due diligence can be measured, it is believed that the Applicant acted with due diligence during this period. Therefore, **zero (0) days** are subtracted from the regulatory review period under paragraph (c)(1). In Applicant's opinion, the marketing applicant acted with clear due diligence as defined under 35 U.S.C. § 156(d)(2)(B) during the above calculated period of paragraphs (c)(2). Thus, **zero (0) days** are subtracted from the regulatory review period of (c)(2).

(iii) According to the above, "one-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section" would be 3,438 days minus 1,093 days, which is 2,345 days. One half of 2,345 days is **1,172.5 days**.

Thus, the adjusted period for (c)(1) of 1,172.5 days is added to (c)(2), which 1,172.5 days plus 304 days, or **1,477 days** (*i.e.*, **4 years and 17 days**).

12.6 37 C.F.R. § 1.775(d)(2)

The number of days determined in paragraph (d)(1) of this section would be **1,477 days**, as described in detail above.

The original term of the patent as shortened by any terminal disclaimer would be 17 years from issue, *i.e.*, **August 12, 2014**.

Thus, adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer would be:

1,413 days added to August 12, 2014, *i.e.,* **August 28, 2018**.

12.7 37 C.F.R. § 1.775(d)(3)

The date of approval of the application under subsection (b) of section 505 of the Federal Food, Drug and Cosmetic Act was November 10, 2004.

Thus, adding 14 years to the date of approval of the application under section 505 of the Federal Food, Drug and Cosmetic Act would be **November 10, 2018**.

12.8 37 C.F.R. § 1.775(d)(4)

The dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section are August 28, 2018 and November 10, 2018, respectively.

Of these two dates, the earlier date is **August 28, 2018**.

12.9 37 C.F.R. § 1.775(d)(5)

(i) The original expiration date of the patent would be August 12, 2014. Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer would result in a date of August 12, 2014 plus 5 years, *i.e.*, **August 12, 2019.**

(ii) The dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section are August 28, 2018 and August 12, 2019, respectively. Of these dates, the earlier date is **August 28, 2018**.

(13) DUTY OF DISCLOSURE

Pronova Biocare AS acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought herein. Pronova acknowledges that multiple applications for patent term extension have been filed (for U.S. Patent Nos. 5,502,007; 5,656,667; and 5,698,594).

(14) FEES

The Director is hereby authorized to charge the amount of $ 1,120.00 (37 C.F.R. § 1.20(j)(l)) to Deposit Account No. 02-4800 for receiving and acting upon the application for extension.

The Director is hereby also authorized to charge any appropriate fee that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

(15) NAME AND ADDRESS FOR CORRESPONDENCE

Please address all inquiries and correspondence relating to this application for patent extension to:

Teresa Stanek Rea
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404
Telephone: (703): 836-6620
Facsimile: (703) 836-2021

(16) MULTIPLE COPIES

This application for extension, together with the appended APPENDICES A through G are being submitted in original form along with three copies. The undersigned hereby certifies that the copies of this application for extension, together with the appended APPENDICES A through G, filed herewith are true and correct copies.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: January 7, 2005

By: _____
Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Attorney's Docket No.: 003301-212
Patent No.: 5,656,667
Application No.: 08/471,200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:

Harald BREIVIK et al.

Application No.: 08/471,200

Patent No.: 5,656,667

Filed: June 6, 1995

For: FATTY ACID COMPOSITION

MAIL STOP: PATENT EXTENSION

TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. § 156

MAIL STOP: PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is an Application for Extension of Patent Term Pursuant to 35 U.S.C. § 156 in connection with the above-identified patent (**an original plus three copies**).

The Director is hereby authorized to charge Deposit Account No. 02-4800 in the amount of $ 1,120.00, which is the requisite fee pursuant to 37 C.F.R. § 1.20(j)(1).

Also enclosed (**an original and three copies**) are the following:

APPENDIX A	Copy of product information about OMACOR® Capsules
APPENDIX B	Copy of approval letter from the FDA for OMACOR® Capsules
APPENDIX C	Copy of U.S. Patent No. 5,656,667
APPENDIX D	Copy of maintenance fee statements for U.S. Patent No. 5,656,667
APPENDIX E	Copy of recorded assignment documents for U.S.S.N. 07/389,902
APPENDIX F	Copy of Request for Recordation of assignment and Copy of Assignment from Norsk Hydro a.s to Pronova Biocare AS regarding U.S. Patent No. 5,656,667
APPENDIX G	Copy of Power of Attorney

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17, 1.20, and 1.21 that may be required by this paper, and to credit any overpayment to Deposit Account No. 02-4800.

This paper is submitted in duplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: January 7, 2005

By: _____
Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

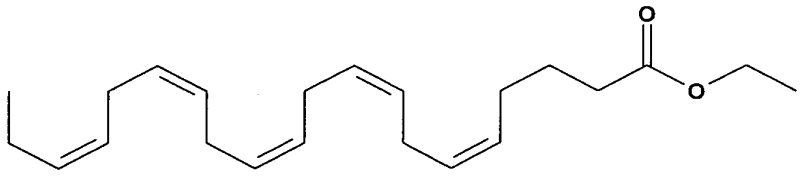
APPENDIX A

(Copy of product information about OMACOR® Capsules)

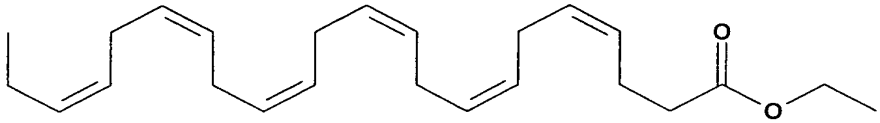
OMACOR®
Omega-3-acid ethyl esters, capsules
Rx only

DESCRIPTION

Omacor®, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor® (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).
The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.
The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.
Omacor® capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of Omacor® is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omacor® may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Omacor®) induced significant, dose–dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor® was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor® in children are not available.

Drug Interactions

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

The effects of Omacor® 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor®, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥ 500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Omacor® 4 g per day reduced median TG, VLDL-C, and non HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor® treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Omacor® on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor® on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor® is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

Usage Considerations

According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor® is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor® therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor® therapy. Omacor® therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients

Omacor® should be used with caution in patients with known sensitivity or allergy to fish.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor® therapy.

In some patients, Omacor® increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor® therapy.

Drug Interactions

Anticoagulants

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor® and concomitant anticoagulants. Patients receiving treatment with both Omacor® and anticoagulants should be monitored periodically.

Cytochrome P450-Dependent Monooxygenase Activities

Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor® to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).
In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 thorough 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omacor is administered to a woman who is breastfeeding.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Omacor® 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Omacor® and 2.6% of patients treated with placebo.

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel–Group Studies for Hypertriglyceridemia That Used Omacor® 4 g per Day

BODY SYSTEM Adverse Event	Omacor® (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

* Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.

CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.

METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.

MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

SKIN: alopecia, eczema, pruritis, and sweating.
SPECIAL SENSES: cataract.
UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Omacor® does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Omacor®, and should continue this diet during treatment with Omacor®. In clinical studies, Omacor® was administered with meals.

The daily dose of Omacor® is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor® (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation OMACOR in bottles of 120 (NDC 0074-5792-01).

Recommended Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze.

Keep out of reach of children.

Distributed by Ross Products Division, Abbott Laboratories, Columbus, OH 43215, USA.

■ Black
■ Pantone Violet
■ PMS 1245
☐ Non-varnish area inside

Label Size: 6.3" x 4"

LOT
EXP

2742M400

N 3 65726 42427 2

NDC 65726-424-27

Omacor®
(omega-3-acid ethyl esters) Capsules

Rx only

120 Capsules

Reliant PHARMACEUTICALS, INC.

Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Do not freeze.

See package insert for complete prescribing information.

Manufactured for:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
by:
Cardinal Health
St. Petersburg, FL 33716

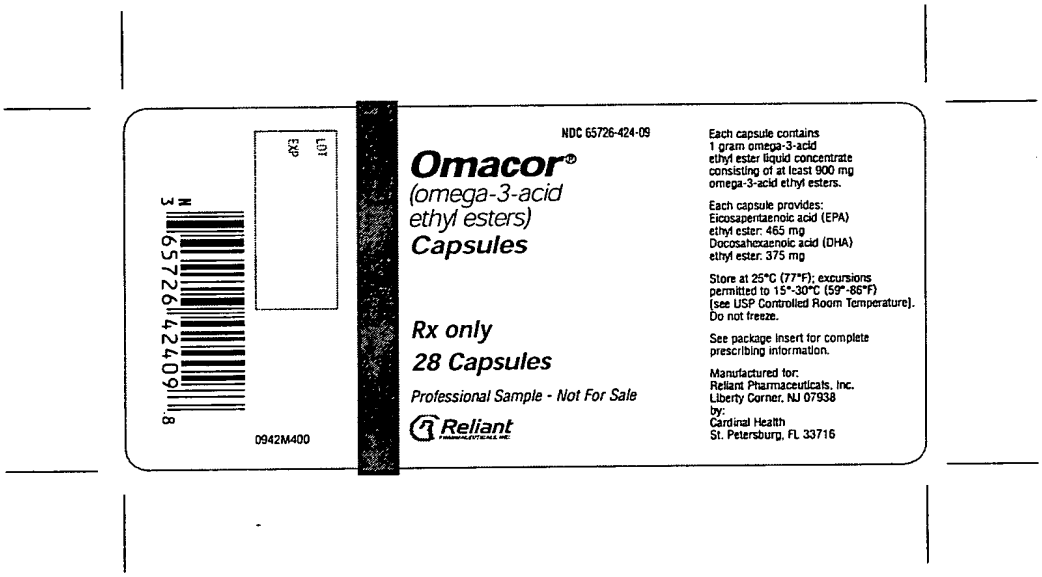
■ Black

■ Pantone Violet

■ PMS 1245

☐ Non-varnish area inside

Label Size: 4.3" x 2.125"



APPENDIX B

(Copy of approval letter from the FDA for OMACOR® Capsules)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654

Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm.D.
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

Dear Dr. Zola:

Please refer to your new drug application (NDA) dated January 9, 2004, received January 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omacor (omega-3-acid ethyl esters) Capsules, 1 g.

We acknowledge receipt of your submissions dated January 20, April 2, May 10, 12, and 24, June 2, July 1 and 20, August 17, September 2, 3, 8, 10, 14, 17, 21, 24, and 29, October 5, 18, 21, 22 (2), 28 (2), and 29, and November 1, 8 (3), 9, and 10, 2004.

This new drug application provides for the use of Omacor (omega-3-acid ethyl esters) Capsules as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with TG levels ≥ 500 mg/dL.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, the application is approved, effective on the date of this letter.
(b) (4)----------

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the immediate container labels submitted November 8, 2004). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-654**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit the content of labeling in electronic format as described in 21 CFR 314.50(l)(5) and in the format described at the following website: http://www.fda.gov/oc/datacouncil/spl.html.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We conclude that your submitted stability data support an 18-month expiry for this product.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of New Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Package Insert
Container Labels: 28 Capsules Professional Sample
120 Capsules

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
11/10/04 04:01:55 PM

APPENDIX C

(Copy of U.S. Patent No. 5,656,667)

US005656667A

United States Patent [19]

Breivik et al.

[11] Patent Number: 5,656,667

[45] Date of Patent: Aug. 12, 1997

[54] FATTY ACID COMPOSITION

[75] Inventors: **Harald Breivik**, Skjelsvik; **Bernt Børretzen**, Porsgrunn; **Knut Helkås Dahl**, Ulefoss; **Hans Einar Krokan**, Sjetnemarka; **Kaare Harald Bønaa**, Tromsø, all of Norway

[73] Assignee: **Norsk Hydro as**, Oslo, Norway

[21] Appl. No.: **471,200**

[22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 902,500, Jun. 23, 1992, Pat. No. 5,502,077, which is a continuation of Ser. No. 389,902, Aug. 4, 1989, abandoned.

[30] **Foreign Application Priority Data**

Aug. 11, 1988 [GB] United Kingdom 8819110

[51] **Int. Cl.**^{6} **A61K 31/20**

[52] **U.S. Cl.** **514/560**; 514/824

[58] **Field of Search** 514/560, 824

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Kimberly Jordan

Attorney, Agent, or Firm—Fitzpatrick, Cella, Harper & Scinto

[57] **ABSTRACT**

Fatty acid composition comprising at least 80% by weight of omega-3-fatty acids, salts or derivatives thereof, wherein (all-Z)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z)-4,7,10,13,16,19-docosahexaenoic acid comprises at least 75% by weight of the total fatty acids. The compositions can be used for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases.

63 Claims, No Drawings

FATTY ACID COMPOSITION

This application is a continuation of application Ser. No. 07/902,500 filed Jun. 23, 1992, now U.S. Pat. No. 5,502,077, which in turn is a continuation of application Ser. No. 07/389,902 filed Aug. 4, 1989, now abandoned.

Present invention relates to a fatty acid composition comprising at least 80% by weight of omega-3 polyunsaturated fatty acids, wherein at least 75% by weight of the total fatty acids comprise omega-3 (all-Z)-5,8,11,14,17-eicosapentaenoic acid (EPA) C 20:5 and (all-Z)-4,7,10,13,16,19-docosahexaenoic acid (DHA) C 22:6.

FIELD OF INVENTION

Cardiovascular diseases leading to morbidity and premature mortality is related to several risk factors such as hypertension, hypertriglyceridemia, hypercholesterolemia, high blood platelet aggregation and according to recent findings, a high activity of the blood coagulation factor VII phospholipid complex. Over the last three decades antihypertensive drugs have contributed to the decline in cardiovascular disease-related morbidity and mortality. There is however heightened concern about side effects and toxicity associated with the current antihypertensive therapy, especially in the mild hypertensive patient. There are results indicating that although the presently used antihypertensive agents are efficient in reducing blood pressure the pulse rate is coincidentally enlarged. Thus there is a need for a drug with fewer adverse effects for the treatment of hypertension. It would be particularly advantageous if such a drug could be used for the simultaneous treatment of all the above mentioned multiple risk factors associated with cardiovascular diseases, which is generally not the case with the currently available antihypertensive drugs.

DESCRIPTION OF PRIOR ART

During the last decade numerous publications have appeared which report that various dietary fish oil preparations containing omega-3 polyunsaturated fatty acids have an effect on serum cholesterol and blood platelet aggregation. The mechanisms suggested for these effects often center around the prostanoid system. Thus there is some information on how dietary fish oils alter the excretion of some prostaglandin metabolites but available data conflict on several points.

A reduction of blood pressure has been reported after intake of fish, crude fish oil (starting at 7% EPA and 5% DHA) or slightly concentrated fish oil preparations (typically containing 18% EPA and 12% DHA) although the components responsible for these effects were never identified. Furthermore all the studies presented so far had one or more serious flaws as pointed out in reviews of the available studies [H. R. Knapp et al., Proceedings of AOCS Short Course on polyunsaturated Fatty Acids and Eicosanoids, Ed. W. E. M. Lands, pp.41–55, American Oil Chemists Society] and [K. Bønaa, Tidskr. Nor Lægeforen nr. 28,1987, 2425–8].

Eicosapentaenoic acid C 20:5 omega 3 (EPA) has been considered to be the most important of the marine omega-3 polyunsaturated fatty acids partly because of its potent antiaggregatory action i.a. reported in U.S. Pat. No. 4,097,602, Silver et al, which was filed in August 1974. Later Dyerberg et al also described the same effect in [Lancet, p.152, Jan. 21, 1978] and [Lancet II, p 117–119, Jul. 15, 1978]. The main reason for the assumed importance of EPA is probably that it belongs to the eicosanoids, which are key substances for the prostaglandin metabolism.

However, according to several recent reports, EPA alone does not have a significant effect on hypertension. In ["Effects of highly purified eicosapentaenoic acid to angiotensin II and norepinephrine in the rabbit", Prostaglandins August 1986, Vol. 32, No 2, pp 179–187] no reduction of blood pressure in rabbits was obtained using highly purified EPA of 90% concentration. [Terano et al, Atherosclerosis, 46, 321–331, (1983)] reported that a preparation containing 75% EPA and 6.2% DHA had no significant effect on blood pressure in healthy volunteers after an intake of 3.6 g EPA ethyl ester. Similarly, [Yoshida et al, Artery, 14, 295–303, 1987]. reported no effect on basal blood pressure after intake of 900 mg EPA ethyl ester for 14 days or more. Furthermore 90% EPA methyl ester had no effect on spontaneously hypertensive rats. [K. Yin et al, 1988, Clinical and Experimental Pharmacology and Physiology 15, 275–280].

In contrast to this, British patent application 2197199 describes a composition for combatting pregnancy-induced hypertension where the compositions used in the example had an EPA content of 28–35%. The patients had no earlier history of hypertension. Hypertension being developed under pregnancy is considered to have different biological causes than normal hypertension, which seems to be underlined by the fact that it usually disappears after the termination of the pregnancy.

To our knowledge there is nothing to suggest that DHA alone has any effect on the blood pressure.

According to U.S. Pat. No. 3,082,228 based on an application filed Dec. 18, 1959 a product containing at least 60% polyunsaturated fatty acids having 20 C atoms or more lowers the blood cholesterol content significantly. Although other early studies indicate that fish oils lower total cholesterol and LDL-cholesterol and raises HDL-cholesterol, later results have generally drawn the opposite conclusion, as pointed out by W. S. Harris in [(n-3)news, 3 (4), 1–7]. Thus, when summarizing 45 articles on the subject, he found that LDL-cholesterol was increased by 2–30% depending on the type of hyperlipidaemia.

From PCT/WO 87/02247 is known a lipid emulsion for parenteral use comprising an emulsifier, water and a marine oil comprising at least one omega-3 fatty acid wherein the concentration of the free fatty acid in the emulsion is below about 5 meq/l, and wherein the marine oil will contain at least 30% by weight of a combination of esters of EPA and DHA. This lipid emulsion is used for the intravenous treatment of thrombotic disease states.

SUMMARY OF THE INVENTION

It has now been found that fatty acid compositions containing a high concentration, of at least 80% by weight, of omega-3 fatty acids, salts or derivatives thereof, where EPA and DHA are present in relative amounts of 1:2 to 2:1, and constitute at least 75% of the total fatty acids, has a surprisingly advantageous effect on all the above mentioned risk factors for cardiovascular diseases, but especially a good effect on mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. It lowers serum LDL-cholesterol, increases serum HDL-cholesterol, lowers serum triglycerides, lowers systolic and diastolic blood pressure and the pulse rate and lowers the activity of the blood coagulation factor VII-phospholipid complex. Although the detailed biological mechanisms for the effects of the compositions according to present application are not explicitly known, there are indications of a surprising synergism between the action of EPA and of DHA.

One advantage of the compositions according to the present application is their being very well tolerated, not giving rise to any severe side effects.

An especially preferred composition according to the present application comprises at least 90% by weight of long chain, polyunsaturated omega-3 fatty acids of which EPA and DHA constitute at least 85% by weight of the total fatty acids and are present in a ratio of EPA:DHA from 1:1 to 2:1 especially about 3:2.

In order to isolate EPA and DHA in a mixture of high concentration according to the present invention, a special method was developed for purifying and isolating the long chain fatty acids from natural fish oils. Compositions according to present application may be produced according to the method of our European Patent Application No.86906964.1. The analysis in % by weight was based on the ethyl esters even if other derivatives or salts or the acids themselves are a part of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The composition according to this invention is preferably produced via the following method. Initially the marine oil raw material is esterified and concentrated via urea fractionation or the like, where the conditions are sufficiently mild to avoid disintegration of the products. The second stage is a molecular distillation.

The fractionation in principle initially removes the major part of the esters having chain length below C 20. Thereafter a main fraction is removed consisting essentially of esters of the C 20- and C 22 acids. As the urea fractionation removes the saturated and less unsaturated esters, this fraction will contain high concentrations of EPA and DHA, according to the present method at least 75% by weight. The total amount of the long chain omega-3 acids will be at least 80% by weight. Other preferred compositions according to present application contain at least 95% by weight, with the EPA plus DHA content being at least 90% by weight. Another preferred composition according to present application contains at least 85% by weight of the total omega-3 fatty acids and an EPA and DHA amount of at least 80% by weight.

Other omega-3 acids of the C 20, C 21 and C 22 series will be obtained approximately in their original concentrations, e.g. from 3–5% by weight, typically at least 4.5% by weight. Thus the special and odd-numbered omega-3 all-Z 6,9,12,15,19-heneicosapentaenoic acid C 21:5 is normally present in concentrations of at least 1.5% by weight and omega-3 all-Z 7,10,13,16,19-docosapentaenoic acid normally in concentrations of about 3.0% by weight.

After removing the urea precipitate, the solvent used, normally ethanol, is partially or fully removed by evaporation and the esters thus isolated may be further purified by washing with water or a slightly alkaline water solution if the pure esters without contamination of the acids should be isolated.

The free acids may be produced by well known hydrolyzation procedures.

The upgrading of the EPA fraction to obtain a weight ratio of EPA:DHA of from 1:1 to 2:1, especially 3:2 or the upgrading of the DHA fraction to obtain a EPA:DHA weight ratio of from 1:1 to 1:2 may be achieved in the molecular distillation stage. The method also provides the possibility of using supercritical fluid extraction and/or chromatography in the second stage with CO_2 eventually containing a more polar modifier, such as ethanol, in order to concentrate the EPA and/or DHA fraction.

The urea fractionation and the subsequent molecular distillation are performed under gentle conditions to avoid oxidation and/or isomerisation of the highly unstable omega-3 acids. As seen from Table 1 and 2 below, which gives the analysis of products obtained in accordance with the method of this invention, there was not more than 1% of unknown components in the purified product. There are, however, a certain amount of minor products such as C-16 and C-18 acids as will appear from the detailed analysis shown in Table 2.

For the main part these products will be the combined sum of the fraction of fatty acid esters, which are naturally occurring in fish oils, but the concentration of each separate ester in the finished product is less than 0.2%, apart from the omega-3 octadecatetraenoic acid C 18:4 n-3, which is present in approximately the same amount as in the starting material.

Thus it will be understood that the total concentration of by-products occurring from the process is very low.

The process is flexible enough to affect the relative proportions between the long chain C 20, C 21 and C 22 fatty acids which occur naturally in available fish oil raw materials. It provides not only for the upgrading of the individual acids, but the ratio between them will remain within a pattern of variation which is optimal in nature. But simultaneously there is room for compensating the sometimes extreme variations which may occur naturally, cfr. below. Thus it will be possible to make a product with a constant and predetermined composition.

Fish oils may also contain by-products and contaminants such as pesticides, chlorinated hydrocarbons, heavy metals, cholesterol and vitamins. During the production of the concentrate, the concentrations of these components are significantly reduced compared to untreated fish oils.

In nature the relative contents of EPA and DHA, and also of the other long chain omega-3 acids, is dependent on the marine species and there are also seasonal variations within the same species. In the USA fish oil is today mainly produced from menhaden. This oil will typically contain 14–19% EPA and 5–8% DHA. Our analysis of one cod liver oil batch showed a content of 6.9 EPA and 8.4 DHA. For capelin the EPA values varied from 8.6 to 11.4 from January 1973 to August 1973, while the DHA values from 6.7% to 11% during the same period. For Norwegian coastal herring the content in October 1973 was 6.4% EPA and 9.8% DHA, while catches in November 1983 showed a reduction to 1.7% and 1.1%, respectively.

These variations mean that dietary intake of fish oils or fish alone, will not secure a constant supply of omega-3 acids. Even if all the long chain C 20, C 21 and C 22 omega-3 acids will not or only may become moderately upgraded during the process, they will be preserved at least in their original proportions.

In Table 1 the left hand column illustrates the typical variations between the contents of individual long chain acids in the compositions of this invention, while the right hand column shows the exact analysis of the test sample used in the study on the biological effects, the results of which are shown in the Tables 4–8 below.

TABLE 1

	Typical product variation	Test Sample
C 20:4 omega-6	1–2	1.4
C 20:5 omega-3	40–60 wt %	54 wt %
C 21:5 omega-3	1–4 wt %	1.5 wt %
C 22:5 omega-3	1–3 wt %	2 wt %
C 22:6 omega-3	25–45 wt %	32.6 wt %
lower acids	3–8.5 wt %	7.5 wt %
unknown	1 wt %	1 wt %
sum Omega-3 FA		90.1 wt %
sum EPA + DHA		86.6 wt %
EPA:DHA		3.3:2

TABLE 2

Table 2 shows a detailed analysis of a batch of starting material and of another composition of this invention obtained therefrom.

Fatty acid	Fatty acid composition (%) Starting material Fish oil,	Product ethyl ester test sample
C14:0	7.6	0.0
Pristanate	0.4	0.0
C16:0	19.1	0.0
C16:1 n7	7.2	0.0
7-Me16:0	0.3	0.0
C16:2 n6	0.5	0.0
C16:2 n4	1.2	0.0
Phytanate	0.3	0.0
C16:3 n4	0.5	0.0
C16:4 n1	1.0	0.2
C18:0	2.3	0.0
C18:1 n9	9.1	0.0
C18:1 n7	3.0	0.0
C18:1 n5	0.4	0.1
C18:2 n6	1.1	0.0
C18:2 n4	0.2	0.0
C18:3 n6	0.2	0.2
C18:3 n3	0.7	0.2
C18:4 n3	2.5	2.8
C18:4 n1	0.1	0.2
C20:1 n9 + 7	5.9	0.0
C20:1	0.1	0.0
C20:2 n6	0.2	0.1
C20:3 n6	0.1	0.0
C20:4 n6	0.7	1.4
C20:4 n3	1.2	0.9
C20:5 n3	16.5	53.4
C22:1 n11 + 9	4.6	0.0
C22:2 n6	0.7	0.0
C21:5 n3	0.9	1.6
C22:4 n6	0.1	0.0
C22:5 n6	0.1	0.4
C22:5 n3	2.0	3.1
C22:6 n3	7.9	34.3
Sum unknown	1.0	1.0
Sum omega-3 FA	31.7	95.4
incl. C 18	3.2	3.0
Sum EPA + DHA	24.4	87.7
EPA:DHA	2.1:1	3.1:2

TABLE 3

Table 3 shows the main fatty acid contents of several compositions according to present application.

Fatty acid	Composition (%)					
C18:2 n6	0.3	0.3	0.1	0.0	0.2	0.1
C18:3 n3	0.3	0.3	0.0	0.1	0.3	0.0

TABLE 3-continued

Table 3 shows the main fatty acid contents of several compositions according to present application.

Fatty acid	Composition (%)					
C18:4 n3	2.3	2.3	3.6	2.2	1.8	0.7
C18:4 n1	0.2	0.2	0.4	0.3	0.0	0.0
C20:4 n6	1.7	1.7	1.5	3.9	1.6	1.6
C20:4 n3	2.4	0.9	1.3	1.2	1.9	0.3
C20:5 n3	54.7	52.7	42.2	48.5	41.0	31.7
C21:5 n3	2.1	2.1	1.7	2.0	1.7	1.2
C22:5 n6	0.4	0.4	0.6	0.8	0.7	1.1
C22:5 n3	5.4	5.8	2.8	4.3	5.8	3.3
C22:6 n3	28.7	31.0	38.0	34.9	42.4	58.5
Sum n3FA incl. C 18	95.9	95.1	89.6	93.2	94.9	95.7
Sum EPA + DHA	83.4	83.7	80.2	83.4	83.4	90.2
EPA:DHA	1.9:1	1.7:1	1.1:1	1.4:1	1:1	1:1.8

n3FA denotes omega-3 fatty acids

BIOLOGICAL EFFECTS

In order to evaluate the effect of a composition according to present application on blood pressure, pulse rate, triglyceride levels, serum cholesterol and HDL-cholesterol, blood platelet aggregation and the coagulation factor VII phospholipid complex activity, the whole population aged 34–60 years, of a small Norwegian town was invited to a health check and of those, 22000 persons were screened for the following criteria:

untreated moderate hypertension of a diastolic blood pressure (DBP) ranging from 89 to 111 mm Hg and a systolic blood pressure (SBP) from 110 to 180 mm Hg.

no previous cardiac illness and not using cardiac drugs

no severe diseases

not extremely overweight

no alcoholism

serum cholesterol of at least 6.0 mmol/liter

The group of volunteers selected by these criteria amounted to 172 persons. The volunteers were screened during a run-in period of 6 month to ensure stabilization of blood pressure before the test substance was administered.

All blood pressure measurements were done with an automatic instrument (Dinamap) and at each occasion three measurements (with 2 minutes intervals) were done sitting and standing under controlled conditions. The average of the two last sitting and standing measurements were used.

The study was a controlled double blind one. The 172 volunteers were randomized to two groups of similar size. One group was treated with placebo capsules of corn oil, each with 1 g corn oil added 0.3% Vitamin E. The other group received capsules containing 1 g of the test substance whose composition is given in Table 1. Both sets of capsules were made of coloured soft gelatin to assure the blind effect. The volunteers were asked to take 3 capsules twice daily of either the test or control substance for 11 to 12 weeks. 171 volunteers completed the study and on average about 90% of the capsules were taken.

As will appear from tables 4 and 5 below, corn oil had no statistically significant effect on the blood pressure. The effect on the test substance on blood pressure was assessed first on the whole group taking the test substance and next on those individuals with higher blood pressures. The average blood pressures for the patients with higher blood pressures at the start and finish of the treatment with the active test substance of this invention are given in Table 4 (diastolic blood pressure) and Table 5 (systolic blood pressure).

TABLE 4

EFFECT OF TEST SUBSTANCE AND CORN OIL ON DIASTOLIC BLOOD PRESSURE

DBP Range	Number of patients	Average DBP before treatment (mm HG)	Average DBP after treatment (mm Hg)	Average Reduction in DBP (mm Hg)	Significance
Test substance					
85-109	62	95.8	93.4	2.4	$p < 0.05$
98-109	22	102	96.2	5.8	$p < 0.01$
Corn oil					
85-109	57	95.7	96.0	0	n.s.
98-109	26	101.8	100.7	1.1	n.s.

n.s. means not significant

TABLE 5

EFFECT OF TEST SUBSTANCE AND CORN OIL ON SYSTOLIC BLOOD PRESSURE

SBP of patients (mm Hg)	Number of patients	Average SBP before treatment (mm HG)	Average SBP after treatment (mm Hg)	Average Reduction in SBP (mm Hg)	Significance
Test substance					
>135	71	148.1	144.5	3.6	$p < 0.05$
>150	24	158.4	150.3	8.1	$p < 0.001$
>155	15	162.2	152.4	9.8	$p < 0.001$
Corn oil					
>135	62	148.5	149.6	0	n.s.
>150	23	159.1	158.0	1.1	n.s.
>155	17	161.8	159.6	2.2	n.s.

As is evident from the above tables, the test substance had a highly significant hypotensive effect both on systolic and diastolic blood pressure. It is also clear that the effect is strongest on those patients with the highest blood pressure. No significant effect was obtained in the corn oil group.

TABLE 6

EFFECT OF TEST SUBSTANCE AND CORN OIL ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE ACCORDING TO DIETARY INTAKE OF FISH (DISHES PER WEEK)

Dishes per week	Number of patients		Average BP before treatment (mm HG)	Average BP after treatment (mm Hg)	Average Reduction in BP (mm Hg)	Significance
Test substance						
0–2	44	SBP	145.3	139.3	−6.9	$p = 0.005$
		DBP	99.8	94.0	−5.7	$p = 0.0001$
3–5	34	SBP	143.6	141.2	−2.4	$p = 0.2$
		DBP	97.7	96.3	−1.4	$p = 0.2$
Corn oil						
0–2	34	SBP	145.2	146.8	+1.6	$p = 0.4$
		DBP	98.3	100.2	+1.9	$p = 0.1$
3–5	44	SBP	142.3	143.4	+1.1	$p = 0.5$
		DBP	97.4	97.9	+0.5	$p = 0.7$

As appears from Table 6 a good hypotensive effect is achieved with the composition according to present application, surprisingly so even in the group with a high dietary intake of fish of 3–5 dishes per week. In comparison, no beneficiary effect is achieved with corn oil.

The results shown above indicate that a composition according to present application gives a surprisingly much better effect than a dietary intake of fish or slightly concentrated marine oil would lead one to expect. This is probably due to a synergistic effect of EPA and DHA.

Compared with the test results achieved in the previously conducted studies with a dietary intake of marine fish oils, the results achieved with a composition according to the present application show a surprising improvement in effect on diastolic and systolic bloodpressure of a slightly hypertensive patient and a more hypertensive patient of respectively approximately 30% and 45%.

TABLE 7

EFFECT OF TEST SUBSTANCE AND CORN OIL ON PULSE RATE (per minute)

Group	Before	After	Change	Significance
Test subst				
sitting	75.4	73.2	−2.2	$p < 0.02$
standing	82.9	80.2	−2.7	$p < 0.005$
Corn Oil				
sitting	74.3	75.1	+0.8	$p = 0.3$
standing	80.9	82.2	+1.3	$p = 0.2$

The pulse rate study included 78 persons in the group recieving the test substance and 77 persons in the other group.

As will appear from the Table above there was obtained a significant lowering in pulse rate with the test substance according to present application and a slight not significant raise of pulse rate with corn oil.

TABLE 8

EFFECT OF TEST SUBSTANCE AND CORN OIL ON SERUM CHOLESTEROL [mmol/liter]

	BEFORE		AFTER	
GROUP	Tot. chol.	HDL Chol.	Tot. Chol.	HDL Chol.
All Patients:				
Test substance (n = 78)	6.58	1.35	6.57	1.41**
Corn oil (n = 78)	6.68	1.33	6.64	1.41**
Tot. Chol. > 7				
Test substance (n = 26)	7.74	1.53	7.31**	1.58*
Corn oil (n = 20)	7.66	1.26	7.45*	1.32*

*$p < 0.1$
**$p < 0.01$

As appears from Table 8 the test composition according to present application lowers total serum cholesterol significantly in patients with a total cholesterol of above 7.0 mmol/liter and raises HDL cholestrol significantly in the whole population. Similar, but weaker effects are obtained in the corn oil group.

The compositions according to present application further lower LDL-cholesterol by 5–10% in patients with total cholesterol>7 mmol/l but has no significant effect in patients with a total cholesterol of <6.5 mmol/l.

TABLE 9

EFFECT OF TEST SUBSTANCE AND CORN OIL ON SERUM TRIGLYCERIDE

Group	n	Before	After	Reduction	p-value
		Triglyceride (mmol/l)			
TEST SUBSTANCE	87	1.51	1.20	0.31	0.001
CORN OIL	85	1.57	1.47	0.03	NS
		Patients with triglycerides > 2.00 mmol/l			
TEST SUBSTANCE	14	3.28	2.03	1.25	0.0001
CORN OIL	17	3.22	2.66	0.56	0.01

As appears from Table 9, the test substance has the effect of lowering the level of serum triglycerides, especially in patients with high levels (>2.0 mmol/l) before treatment. No significant effect is obtained with corn oil in the whole group of volunteers, whereas a very small effect is obtained in persons with high levels of triglycerides.

TABLE 10

EFFECT OF TEST SUBSTANCE AND CORN OIL ON BLOOD PLATELET AGGREGATION

		Collagen 0,2 ug/ml				Collagen 0,1 ug/ml			
		Before		After		Before		After	
Group	n	$\bar{X}$	SEM	$\bar{X}$	SEM	$\bar{X}$	SEM	$\bar{X}$	SEM
TEST SUBST	21	63.4 ± 4.40		38.8 ± 5.19		38.0 ± 5.91		13.7 + 3,77	
CORN OIL	21	73.5 ± 4.40		57.4 ± 6.37		43.4 ± 45.5		15.2 ± 3.32	

As will appear from Table 10, the compositions according to present application have a blood platelet antiaggregating effect.

The coagulation factor VII-phospholipid complex is found in the plasma from men belonging to a high risk group for cardiovascular diseases, as described in [P. Leren et al, The Oslo Study, Cardiovascular diseas in middle aged and young Oslo men. *Acta Med. Scand.* suppl.588,1–38, (1987)] and [Dalaker et al, A novel form of factor VII in plasma from men at risk for cardiovascular disease, *Br. J. Haematol.*, 61, 315–322, (1985)], and is considered to be another risk factor for cardiovascular disease.

TABLE 11

EFFECT OF TEST SUBSTANCE AND CORN OIL ON COAGULATION FACTOR VII PHOSPHOLIPID COMPLEX ACTIVITY (PERCENT)

Group	n	Before	After	Difference
TEST SUBST	69	9.7	6.6	3.1**
CORN OIL	72	8.5	8.8	0.3 N.S.

**p < 0.02

As appears from the table the activity is reduced significantly with the composition according to the present application, whereas no significant effect is reached with corn oil.

According to the results shown in the tables 3–11 above, a composition according to present application has a significant effect on all the above mentioned risk factors for cardiovascular diseases. In comparison some positive results are obtained with corn oil but no significant effect is obtained for blood pressure, the level of serum triglycerides or for the activity of the coagulation factor VII. Further the effects measured in the corn oil group for these risk factors seem to be going in the opposite direction, being detrimental.

Thus fatty acid compositions according to the present invention are potentially valuable for the treatment and prophylaxis of multiple risk factors known for cardiovascular diseases, such as hypertension, hypertriglyceridemia and high coagulation factor VII phospholipid complex activity.

The doses of the composition of this invention needed for therapeutic or prophylatic effect will vary with the type of administration. In our large scale tests we administered 6 grams per person per day of the test composition. Generally for the average adult person the doses may vary from 1.0 to 10 grams depending upon body size and the seriousness of the condition to be treated.

The compositions according to the present application may further be used as an additional drug to the customary hypertensive drug in treatment of hypertension. The doses will presumably lie in the lower part of the above mentioned dosage range.

Other possible medical indications for which the compositions according to the present application may be administrered are chronic polyarthritis, psoriatic artheritis, periarteritis nodosa, lupus erythematosus disseminatus (LED), sclerodermia, Crohn's disease, ulcerative colitis, psoriasis, atopic dermatitis and migraine as has been indicated in standard in vivo tests.

Perferably the active compounds should be orally administered in the form of pills, soft capsules or the like. However, the administration could also be through any other route where the active ingredients may be efficiently absorbed and utilized, e.g. intravenously, subcutaneously, rectally, vaginally or possibly topically.

The pharmaceutical composition may eventually comprise, in addition to the EPA and DHA active ingredients as defined, one or more pharmaceutically acceptable carriers as well known in the art. The compositions can also include fillers, stabilizers, extenders, binders, humidifiers, surfactants, lubricants and the like, as known in the art of formulating pharmaceutical composition.

In addition antioxidants, for example hydroxytoluene, butyrate, quinone, tocopherol, ascorbic acid etc., preservatives, colouring agents, perfumes, flavourings and other pharmaceutical agents may be used.

EXAMPLE OF PHARMACEUTICAL PREPARATION

Soft Gelatine Capsules Containing 1 g/per Capsule

Composition:

EPA ethyl eater	525 mg/capsule
DHA ethyl ester	315 mg/capsule
d-alpha Tocopherol	4 IU/capsule
Gelatine	246 mg/capsule
Glycerol	118 mg/capsule
Red iron oxide	2.27 mg/capsule
Yellow iron oxide	2.27 mg/capsule

The active ingredients and the excipients are weighed and homogenized on a high speed stirrer. The mixture is then colloid milled and deareated in a stainless steel vessel ready for encapsulation. The mixture is filled in soft gelatine capsules of size 20 oblong (average weight 1.4 g) using a standard capsulation machine.

What is claimed is:

1. A method for elevating the HDL cholesterol level in the serum of a human patient, which comprises administering to the patient a pharmaceutical composition in which the active ingredients consist essentially of a mixture of fatty acids of which at least 80% by weight is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, said composition being administered in amounts providing a daily dosage of 1 to 10 grams of said mixture of fatty acids.

2. The method of claim 1, wherein at least 85% by weight of the mixture of fatty acids is comprised of long chain omega-3 fatty acids.

3. The method of claim 2, wherein the EPA constitutes 40 to 60% by weight of the mixture of fatty acids and the DHA constitutes 25 to 45% by weight of the mixture of fatty acids.

4. The method of claim 3, wherein the EPA and DHA are present in the composition in an EPA:DHA weight ratio of from 1:1 to 2:1.

5. The method of claim 4, wherein at least 3% by weight of the mixture of fatty acids is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

6. The method of claim 4, wherein at least 1% by weight of the mixture of fatty acids is comprised of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid.

7. The method of claim 6, wherein at least 85% by weight of the fatty acid content of the composition is comprised of the combination of EPA and DHA, and the fatty acids are present in the composition in ethyl ester form.

8. The method of claim 4, wherein the composition is administered orally.

9. The method of claim 4, wherein at least 4.5% by weight of the mixture of fatty acids is comprised of fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

10. The method of any of claims 5, 6, or 9, wherein the fatty acids are present in the composition in esterified form.

11. The method of any of claims 5, 6, or 9, wherein the fatty acids are present in the composition in ethyl ester form.

12. The method of any of claims 5, 6, or 9, wherein the fatty acids are present in the composition in salt form.

13. The method of any of claims 5, 6, or 9, wherein the fatty acids are present in the composition in the free acid form.

14. A pharmaceutical mixed-fatty-acids composition in which

a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and

b) (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight.

15. The composition of claim 14, wherein at least 85% by weight of the composition is comprised of long chain omega-3 fatty acids.

16. The composition of claim 15, wherein the EPA constitutes 40 to 60% by weight of the composition and the DHA constitutes 25 to 45% by weight of the composition.

17. The composition of claim 16, wherein C 20:4 omega-6 fatty acid constitutes at least one percent by weight of the composition.

18. The composition of claim 17, wherein C 22:5 omega-3 fatty acid constitutes at least one percent by weight of the composition.

19. The composition of claim 16, wherein the (all-Z omega-3) -6,9,12,15,18-heneicosapentaenoic acid is present in an amount of from 1 to 4% by weight.

20. The composition of any of claims 17, 18, or 19, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

21. The composition of claim 19, wherein C 22:5 omega-3 fatty acid constitutes 1 to 3% by weight of the composition.

22. The composition of claim 21, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

23. The composition of any of claims 14, 15, or 16, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

24. A mixed-fatty-acids composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases in which

a) at least 80% by weight of the composition is comprised of omega-3 fatty acids,

b) at least 80% by weight of the total fatty acid content of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, and

c) omega-3 fatty acids other than EPA and DHA are present in an amount of at least 1.5% by weight of the total fatty acids.

25. The composition according to claim 24, wherein other long chain fatty acids present are selected from the group consisting of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid, (all-Z omega-3)-7,10,13,16,19-docosapentaenoic acid, and (all-Z omega-3)-6,9,12,15-octadecatetraenoic acid.

26. The composition of any of claims 14, 22, or 25, wherein the fatty acids are present in ethyl ester form.

27. The composition of any of claims 14, 22, or 25, wherein the fatty acids are present in the free acid form.

28. A pharmaceutical mixed-fatty-acids composition in which

a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and

b) at least 3% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

29. The composition of claim 28, wherein 3 to 5% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

30. The composition of claim 28, wherein at least 85% by weight of the composition is comprised of long chain omega-3 fatty acids.

31. The composition of claim 30, wherein the EPA constitutes 40 to 60% by weight of the composition and the DHA constitutes 25 to 45% by weight of the composition.

32. The composition of claim 31, wherein C 20:4 omega-6 fatty acid constitutes at least one percent by weight of the composition.

33. The composition of claim 31, wherein C 22:5 omega-3 fatty acid constitutes at least one percent by weight of the composition.

34. The composition of claim 33, wherein C 22:5 omega-3 fatty acid constitutes 1 to 3% by weight of the composition.

35. The composition of claim 34, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

36. The composition of claim 35, wherein the fatty acids are present in the free acid form.

37. The composition of claim 31, wherein the fatty acids are present in the free acid form.

38. The composition of claim 31, wherein (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight.

39. The composition of any of claims 32, 33, or 38, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

40. The composition of claim 38, wherein the (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of from 1 to 4% by weight.

41. The composition of any of claims 28, 30, or 31, wherein the EPA and DHA are present in an EPA:DHA weight ratio of from 1:1 to 2:1.

42. The composition of any of claims 28, 31, or 35, wherein the composition is in oral dosage form.

43. The composition of any of claims 28, 31, or 35, wherein the fatty acids are present in esterified form.

44. The composition of any of claims 28, 31, or 35, wherein the fatty acids are present in ethyl ester form.

45. The composition of any of claims 28, 31, or 35, wherein the fatty acids are present in salt form.

46. The composition of claim 28, wherein the fatty acids are present in the free acid form.

47. A mixed-fatty-acids composition for the treatment or prophylaxis of multiple risk factors for cardiovascular diseases in which

a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1 and

b) at least 3% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

48. The composition of claim 47, wherein 3 to 5% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms.

49. A pharmaceutical mixed-fatty-acids composition in which

a) at least 90% by weight of the composition is comprised of long chain, polyunsaturated, omega-3 fatty acids;

b) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:1 to 2:1, with the EPA constituting 40 to 60% by weight of the composition and the DHA constituting 25 to 45% by weight of the composition;

c) at least 4.5% by weight of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20, 21, or 22 carbon atoms;

d) from 1 to 4% by weight of the composition is comprised of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid; and

e) the composition is in oral dosage form and includes an effective amount of a pharmaceutically acceptable antioxidant.

50. The composition of claim 49, wherein the fatty acids are present in ethyl ester form.

51. The composition of claim 50, wherein at least 85% by weight of the fatty acid content of the composition is comprised of the combination of EPA and DHA.

52. The composition of either of claims 50 or 51, wherein the antioxidant is tocopherol.

53. The composition of any of claims 14, 22, or 24, wherein the composition is in oral dosage form.

54. The composition of any of claims 14, 22, or 25, wherein the fatty acids are present in esterified form.

55. The composition of claim 54, wherein the fatty acids are present in salt form.

56. The composition according to claim 24 or claim 25, wherein the total concentration of long chain omega-3 fatty acids is at least 90% by weight, the combined weight of the EPA and DHA constitutes at least 85% by weight of the total fatty acids, the EPA and DHA are present in a weight ratio of EPA:DHA of from 1:1 to 2:1, and the other long chain omega-3 C 20, C 21 and C 22 acids constitute at least 4.5% by weight of the composition.

57. The composition according to claim 24, wherein the total concentration of long chain omega-3 fatty acids is at least 95% by weight, the combined weight of the EPA and DHA constitutes at least 90% by weight of the total fatty acids, and the other long chain C 20, C 21 and C 22 acids constitute at least 4.5% by weight of the composition.

58. The composition according to claim 57, wherein EPA and DHA are present in a weight ratio of EPA:DHA of from 1:1 to 2:1.

59. The composition according to claim 24 or claim 25, wherein the total concentration of long chain omega-3 fatty acids is at least 85% by weight and the other long chain C 20, C 21 and C 22 acids constitute at least 4.5% by weight of the composition.

60. The composition according to claim 24, wherein the fatty acids are present in the form of pharmaceutically acceptable salts.

61. The composition according to claim 24, wherein the fatty acids are present in the form of an ester.

62. The composition according to claim 61, wherein the fatty acids are present in the form of ethyl esters.

63. The composition according to claim 61, wherein the ester is an alkyl ester.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,656,667 Page 1 of 4

DATED : August 12, 1997

INVENTOR(S) : Breivik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title Page,

[56] References Cited

OTHER PUBLICATIONS

Line 6, "and Treatment" should read --and "Treatment--;

Line 7, "Group, in" should read --Group", in--; and

Line 27, "11th Ed. (McGraw-hill, New York) p. 1204. (1985)." should read --11th Ed. (McGraw-Hill, New York) p. 1204 (1985).--.

COLUMN 1:

Line 16, "is" should read --are--;

Line 27, "pressure" should read --pressure,--;

Line 28, "enlarged." should read --increased.--;

Line 31, "above" should read --above- --; and

Line 51, "Furthermore" should read --Furthermore,--.

COLUMN 2:

Line 13, "Furthermore" should read --Furthermore,--;

Line 33, "raises" should read --raise--;

Line 37, "2-30%" should read --2-30%,--; and

Line 55, "above mentioned" should read --above-mentioned--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,656,667
DATED : August 12, 1997
INVENTOR(S) : Breivik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

COLUMN 4:

Line 4, "Table 1 and 2" should read --Tables 1 and 2--;

Line 61, "left hand" should read --left-hand--; and

Line 63, "right" should read --right- --.

COLUMN 6:

Line 24, "present" should read --the present--;

Line 41, "6 month" should read --6-months--;

Line 58, "tables 4" should read --Tables 4--; and

Line 60, "on the" should read --of the--.

COLUMN 8:

Line 23, "Test subst" should read --Test substance--;

Line 37, "raise" should read --rise--;

Line 58, "present" should read --the present--; and

Line 65, "has" should read --have--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,656,667
DATED : August 12, 1997
INVENTOR(S) : Breivik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

COLUMN 9

Line 26, change "0,2" to --0.2-- and change "0,1" to --0.1--;

Line 31, change "+3,77" to --±3.77--;

Line 32, change "+45.5" to --±4.55--;

Line 37, change "present" to --the present--;

Line 41, change "diseas" to --disease--;

Line 63, change "tables 3-11" to --Tables 3-11--; and

Line 65, change "above mentioned" to --above-mentioned--.

COLUMN 10

Line 12, change "prophylatic" to --prophylactic--;

Line 13, change "large scale" to --large-scale--; and

Line 21, change "above mentioned" to --above-mentioned--.

COLUMN 11:

Line 52, "2:1 and" should read --2:1, and--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,656,667 Page 4 of 4

DATED : August 12, 1997

INVENTOR(S) : Breivik et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

COLUMN 12:

Line 45, "2:1 and" should read --2:1, and--.

COLUMN 13:

Line 37, "2:1 and" should read --2:1, and--.

COLUMN 14:

Line 22, "claim 54," should read --claim 25,--.

Signed and Sealed this

Thirty-first Day of March, 1998

Attest:

BRUCE LEHMAN

Attesting Officer *Commissioner of Patents and Trademarks*

APPENDIX D

(Copy of maintenance fee statements for U.S. Patent No. 5,656,667)

UNITED STATES DEPARTMENT OF COMMERCE
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225 REINEKERS LANE
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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "STAT", below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE CODE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ATTY DKT NUM
5,656,667	183	$850.00	$0.00	08/471,200	08/12/97	06/06/95	04	NO	PAID	1526.100B

DIRECT YOUR RESPONSE TOGETHER WITH ANY QUESTIONS ABOUTTHIS NOTICE TO:
Mail Stop: M. Correspondence, Director of the United States Patent and Trademark Office
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Alexandria, VA 22313-1450

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "STAT", below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE CODE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ATTY DKT NUM
5,656,667	1552	$2,150.00	$0.00	08/471,200	08/12/97	06/06/95	08	NO	PAID	1526.100B

DIRECT YOUR RESPONSE TOGETHER WITH ANY QUESTIONS ABOUTTHIS NOTICE TO:
Mail Stop: M. Correspondence, Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPENDIX E

(Copy of recorded assignment documents for U.S.S.N. 07/389,902)

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 07389902 **Filing Dt:** 08/04/1989 **Patent #:** NONE **Issue Dt:**

PCT #: NONE **Publication #:** NONE **Pub Dt:**

Inventors: HARALD BREIVIK, BERNT BORRETZEN, KNUT H. DAHL, HANS E. KROKAN, KAARE H. BONAA

Title: FATTY ACID COMPOSITION

Assignment: 1

Reel/Frame: 005111/0097 **Received:** **Recorded:** 08/04/1989 **Mailed:** NONE **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignors: BREIVIK, HARALD **Exec Dt:** 07/17/1989

BORRETZEN, BERNT **Exec Dt:** 07/17/1989

DAHL, KNUT H. **Exec Dt:** 07/27/1989

KROKAN, HANS E. **Exec Dt:** 07/19/1989

BONAA, KAARE H. **Exec Dt:** 07/26/1989

Assignee: NORSK HYDRO A.S., BYGDOY ALLE 2, 0257 OSLO 2, NORWAY

Correspondent: WENDEROTH, LIND & PONACK
SOUTHERN BUILDING - STE. 700
805 FIFTEENTH ST., N. W.
WASHINGTON, DC 20005

Search Results as of: 12/21/2004 12:23:35 P.M.

Assignment

In consideration of the sum of One Dollar ($1.00) and other good and valuable consideration paid to each of the undersigned

Insert Name(s) of Inventor(s)

Harald Breivik, Bernt Børretzen, Knut Helkås Dahl,
Hans Einar Krokan, Kaare H. Bønaa

and

the undersigned hereby sell(s) and assign(s) to

Insert Name of Assignee

Norsk Hydro a.s

Address

of Bygdøy Allé 2, 0257 Oslo 2, Norway

(hereinafter designated as the Assignee) the entire right, title and interest for the United States of America as defined in 35 USC 100, in the invention known as

Title of Invention

Fatty acid composition

for which an application for patent in the United States of America has been executed by the undersigned

Date of Signing of Application

on July 17, 19, 26, and 27, 1989

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such interference.

The undersigned agree(s) to execute all papers and documents and perform any act which may be necessary in connection with claims or provisions of the International Convention for Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States patent to the Assignee.

The undersigned hereby authorize(s) and request(s) the Commissioner of Patents to issue any and all Letters Patents of the United States resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

The undersigned hereby grant(s) the firm of WENDEROTH, LIND & PONACK, Southern Building, Suite 700, 805 Fifteenth Street, N.W., Washington, D.C. 20005, the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent Office for recordation of this document.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date 17 July 1989, Name of Inventor Harald Breivik

Date 17 July 1989, Name of Inventor Bernt Børretzen

Date 27 July 1989, Name of Inventor Knut Helkås Dahl

Date 19 July 1989, Name of Inventor Hans Einar Krokan

Date 26th July 1989, Name of Inventor Kaare H. Bønaa

Date ____, Name of Inventor ____

(This assignment should preferably be acknowledged before a United States Consul. If not, then the execution by the Inventor(s) should be witnessed by at least two witnesses who sign here.)

Witness Marg R. Solberg

Witness Brit Fardal

ACKNOWLEDGMENT

} ss

This ____ day of ____, 19____, before me personally came the above-named ____

to me personally known as the individual(s) who executed the foregoing assignment, who did acknowledge to me that he (they) executed the same of his (their) own free will for the purposes therein set forth.

RECORDED
PATENT & TRADEMARK OFFICE
AUG -4 89

Official Signature

SEAL

Official Title

COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE

The above application may be more particularly identified as follows:

U. S. Application Serial No. ____, Filing Date August 4, 1989

Applicant Reference Number P8844, Atty. Docket No. 201-P8844

Title of Invention FATTY ACID COMPOSITION

APPENDIX F

(Copy of Request for Recordation of Assignment and Assignment from Norsk Hydro a.s to Pronova Biocare AS regarding U.S. Patent No. 5,656,667)

Form-PTO-1595
1-31-92

TRANSMITTAL OF DOCUMENT FOR RECORDATION
PATENTS ONLY

Atty. Docket: 01526.100B

To the Director, U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Norsk Hydro ASA
N–0240 Oslo, Norway

Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Pronova Biocare AS

Foreign Address: Vollsveien 6 (P.O. Box 420)

1327 Lysaker, Norway

Domestic Address: _____

City: _____ State _____ ZIP _____

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: June 8, 2004

4. Application number(s) or patent number(s): U.S. Patent No. 5,656,667
If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application Number: 08/471,200

Filing Date: 06/23/92

B. Title of Invention:

Fatty Acid Composition

Additional numbers attached?
☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name:
Fitzpatrick, Cella, Harper & Scinto

30 Rockefeller Plaza

New York, New York 10112-3800

Telephone No.:
(212) 218-2100

Facsimile No.:
(212) 218-2200

6. Number of applications and patents involved:

One

7. Total fee (37 CFR 3.41): .... $ 40.00

☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit account number (for deficiency or excess)

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9 Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and the attached is the original document or is a true copy of the original document.

John W. Behringer — Name of Person Signing

John W. Behringer — Signature

August 11, 2004 — Date

Total number of pages including cover sheet, attachments, and documents: 3

ASSIGNMENT

The undersigned, *Norsk Hydro ASA, N-0240 Oslo, Norway*, hereby declares to have assigned all rights to our U.S. Patent No. 5,656,667

"Fatty acid composition"

to

Pronova Biocare AS
Vollsveien 6
P.O.Box 420
1327 Lysaker
Norway

so that the patent can be registered in the name of the firm.

Oslo,	Norway	08.06.2004
Place	Country	Date

André Berg
(Witness)

for Norsk Hydro ASA
Svein Hofseth

Head of the Patent & Trade Mark Department

Client

MAIL STOP Assignment Recordation Services
Commissioner for Patents
Washington, D.C. 20231

Date 8 / 11 / 04 (Mo. / Day / Yr.)

Atty. Docket 01526.00100B

Sir:

Kindly acknowledge receipt of the accompanying:

- ☐ Specifications, claims and abstract _____ pages, with Transmittal Form
- ☐ Patent Application Bibliographic Data Sheet _____ sheets
- ☐ Executed Oath or Declaration and Power of Attorney
- ☐ _____ Sheets of _____ formal _____ informal drawings
- ☐ Check for $ _____ (filing fee)
- ☐ Request for Continued Examination and Check for $ _____
- ☒ Assignment, PTO-1595 and Check for $ 40.00 [W] + transmittal
- ☐ Transmittal Under 37 CFR 1.53(d) (CPA)
- ☐ Petition under 37 CFR 1.136 and check for $ _____
- ☐ Other (specify)

by placing your receiving date stamp hereon and mailing or returning to deliverer.

This is a ☐ Continuation ☐ Divisional ☐ Continuation-In-Part

Atty. GWB/BG Due Date N / D / D (Mo. / Day / Yr.)

37 CFR 1.8 ☐
37 CFR 1.10 ☐
By Hand ☐

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WASHINGTON, DC 20006-1110
(202) 530-1010

CHECK NUMBER: 130575 15-7011/2540
CHECK DATE: 08/11/2004
MATTER NUMBER: 01526.00100B.

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COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, 20231

Authorized Signature

APPENDIX G

(Copy Power of Attorney)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP PATENT EXT.**
	)	
Harald BREIVIK et al.	)	Group Art Unit: Unassigned
	)	
Application No.: 08/471,200	)	Examiner: Unassigned
	)	
U.S. Patent No.: 5,656,667	)	Confirmation No.: Unassigned
	)	
Filed: June 6, 1995	)	
	)	
Issued: August 12, 1997	)	
	)	
For: FATTY ACID COMPOSITION	)	

REVOCATION AND NEW POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As the assignee of the above-identified patent, all powers of attorney previously given are hereby revoked, and we hereby appoint Benton S. Duffett, Jr., Registration No. 22,030; Teresa Stanek Rea, Registration No. 30,427; Mercedes K. Meyer, Registration No. 44,939; Susan M. Dadio, Registration No. 40,373, and the attorneys and agents associated with the following PTO Customer Number of Burns, Doane, Swecker & Mathis, L.L.P. to transact all business in the Patent and Trademark Office connected with this patent and to transact all business in connection with the above-identified patent:

Customer Number **2 1 8 3 9**

The Assignee has reviewed documentary evidence of the change of title from the original owner to the Assignee recorded in the U.S. Patent and Trademark Office at the following Reel(s) and Frame(s) and attached copy of assignment submitted for recordation with the U.S. Patent and Trademark Office on August 11, 2004. Assignee certifies that to the best of its knowledge and belief it is the owner of the entire right, title, and interest in and to the above-identified patent, the application for which is a continuation of U.S. Serial No. 07/902,500, filed June 23, 1992, now U.S. Patent No. 5,502,077, which is a continuation of U.S. Serial No. 07/389,902 filed August 4, 1989, now abandoned; U.S. Patent No. 5,656,667 is encompassed by the Assignment for U.S. Serial No. 07/389,902 recorded at: Reel 005111, Frame 0097.

Please direct all telephone calls and correspondence to:

BURNS, DOANE, SWECKER & MATHIS, L.L.P.
Customer Number 2 1 8 3 9
P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

The undersigned is empowered to sign this statement.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: Dec 29th 2004

By: _____
Name: Geir Bond
Title: CEO

Pronova Biocare AS
Vollsveien 6
P.O. Box 420
1327 Lysaker
Norway

Form-PTO-1595
1-31-92

TRANSMITTAL OF DOCUMENT FOR RECORDATION
PATENTS ONLY

Atty. Docket: 01526.100B

To the Director, U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Norsk Hydro ASA
N–0240 Oslo, Norway

Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Pronova Biocare AS

Foreign Address: Vollsveien 6 (P.O. Box 420)

1327 Lysaker, Norway

Domestic Address: _____

City: _____ State _____ ZIP _____

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: June 8, 2004

4. Application number(s) or patent number(s): U.S. Patent No. 5,656,667
If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application Number: 08/471,200

Filing Date: 06/23/92

B. Title of Invention:

Fatty Acid Composition

Additional numbers attached?
☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name:
Fitzpatrick, Cella, Harper & Scinto

30 Rockefeller Plaza

New York, New York 10112-3800

Telephone No.:
(212) 218-2100

Facsimile No.:
(212) 218-2200

6. Number of applications and patents involved:

One

7. Total fee (37 CFR 3.41): .... $ 40.00

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To the best of my knowledge and belief, the foregoing information is true and the attached is the original document or is a true copy of the original document.

John W. Behringer
Name of Person Signing

John W. Behringer
Signature

August 11, 2004
Date

Total number of pages including cover sheet, attachments, and documents: 3

DC_MAIN 174530v1

ASSIGNMENT

The undersigned, *Norsk Hydro ASA, N-0240 Oslo, Norway,* hereby declares to have assigned all rights to our U.S. Patent No. 5,656,667

"Fatty acid composition"

to

Pronova Biocare AS
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so that the patent can be registered in the name of the firm.

Oslo,	Norway	08.06.2004
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André Berg
(Witness)

for Norsk Hydro ASA

Svein Hofseth

Head of the Patent & Trade Mark Department

Client

MAIL STOP Assignment
Recordation Services
Commissioner for Patents
Washington, D.C. 20231

Date 8 / 11 / 04
Mo. Day Yr.

Atty. Docket 01526.00100B

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- ☐ Petition under 37 CFR 1.136 and check for $ _____
- ☐ Other (specify)

by placing your receiving date stamp hereon and mailing or returning to deliverer.

This is a ☐ Continuation ☐ Divisional ☐ Continuation-In-Part

37 CFR 1.8 ☐
37 CFR 1.10 ☐
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CHECK DATE: 08/11/2004
MATTER NUMBER: 01526.00100B.

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[illegible]INGTON, 20231

[signature]

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 07389902 **Filing Dt:** 08/04/1989 **Patent #:** NONE **Issue Dt:**

PCT #: NONE **Publication #:** NONE **Pub Dt:**

Inventors: HARALD BREIVIK, BERNT BORRETZEN, KNUT H. DAHL, HANS E. KROKAN, KAARE H. BONAA

Title: FATTY ACID COMPOSITION

Assignment: 1

Reel/Frame: 005111/0097 **Received:** **Recorded:** 08/04/1989 **Mailed:** NONE **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignors: BREIVIK, HARALD **Exec Dt:** 07/17/1989

BORRETZEN, BERNT **Exec Dt:** 07/17/1989

DAHL, KNUT H. **Exec Dt:** 07/27/1989

KROKAN, HANS E. **Exec Dt:** 07/19/1989

BONAA, KAARE H. **Exec Dt:** 07/26/1989

Assignee: NORSK HYDRO A.S., BYGDOY ALLE 2, 0257 OSLO 2, NORWAY

Correspondent: WENDEROTH, LIND & PONACK
SOUTHERN BUILDING - STE. 700
805 FIFTEENTH ST., N. W.
WASHINGTON, DC 20005

Search Results as of: 12/21/2004 12:23:35 P.M.

Assignment

In consideration of the sum of One Dollar ($1.00) and other good and valuable consideration paid to each of the undersigned

Insert Name(s) of Inventor(s)

Harald Breivik, Bernt Børretzen, Knut Helkås Dahl,
Hans Einar Krokan, Kaare H. Bønaa

and

the undersigned hereby sell(s) and assign(s) to

Insert Name of Assignee

Norsk Hydro a.s

Address

of Bygdøy Allé 2, 0257 Oslo 2, Norway

(hereinafter designated as the Assignee) the entire right, title and interest for the United States of America as defined in 35 USC 100, in the invention known as

Title of Invention

Fatty acid composition

for which an application for patent in the United States of America has been executed by the undersigned

Date of Signing of Application

on July 17, 19, 26, and 27, 1989

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such interference.

The undersigned agree(s) to execute all papers and documents and perform any act which may be necessary in connection with claims or provisions of the International Convention for Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States patent to the Assignee.

The undersigned hereby authorize(s) and request(s) the Commissioner of Patents to issue any and all Letters Patents of the United States resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

The undersigned hereby grant(s) the firm of WENDEROTH, LIND & PONACK, Southern Building, Suite 700, 805 Fifteenth Street, N.W., Washington, D.C. 20005, the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent Office for recordation of this document.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date 17 July 1989, Name of Inventor Harald Breivik

Date 17 July 1989, Name of Inventor Bernt Børretzen

Date 27 July 1989, Name of Inventor Knut Helkås Dahl

Date 19 July 1989, Name of Inventor Hans Einar Krokan

Date 26th July 1989, Name of Inventor Kaare H. Bønaa

Date ....., Name of Inventor .....

(This assignment should preferably be acknowledged before a United States Consul. If not, then the execution by the Inventor(s) should be witnessed by at least two witnesses who sign here.)

Witness Marg R. Solberg

Witness Bird Larsen

ACKNOWLEDGMENT

..... } ss
.....

This ..... day of ....., 19....., before me personally came the above-named .....

.....

.....

to me personally known as the individual(s) who executed the foregoing assignment, who did acknowledge to me that he (they) executed the same of his (their) own free will for the purposes therein set forth.

RECORDED
PATENT & TRADEMARK OFFICE
AUG -4 89

SEAL

..... Official Signature

..... Official Title

COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE

The above application may be more particularly identified as follows:

U. S. Application Serial No. ....., Filing Date August 4, 1989

Applicant Reference Number P8844, Atty. Docket No. 201-P8844

Title of Invention FATTY ACID COMPOSITION

.....